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Ring-opening cross metathesis of 1,3-cyclopentadiene-heterodienophile cycloadducts to produce cyclic hydrazines and hydroxylamines

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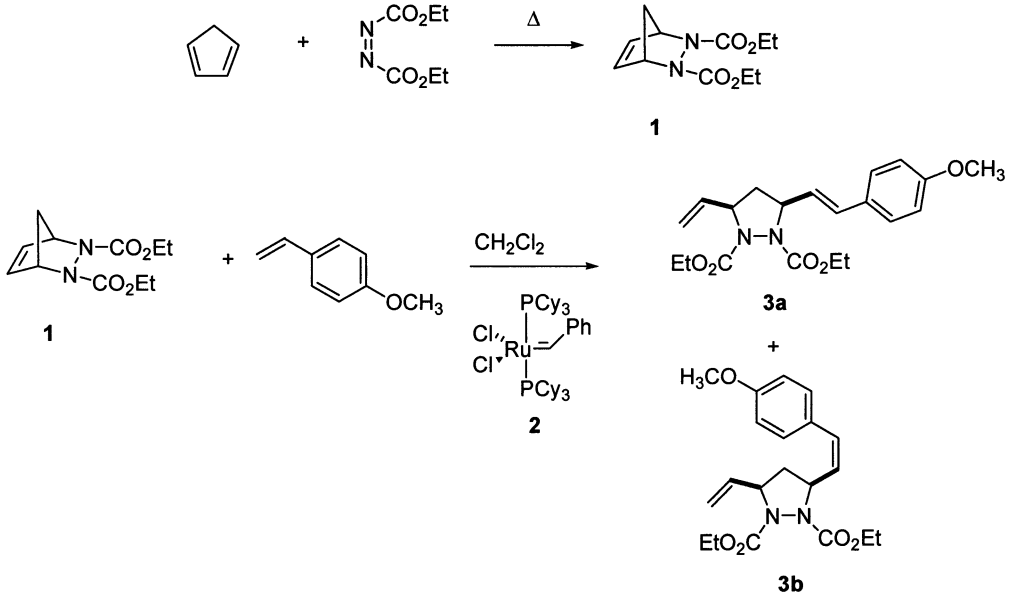
Abstract—The combination of a hetero-Diels–Alder reaction of a N–N or N–O heterodienophile and 1,3-cyclopentadiene with ruthenium catalyzed ring-opening cross metathesis (ROCM) produces new functionalized heterocyclic five-membered rings. The cycloadduct of 1,3-cyclopentadiene and diethyl azidodicarboxylate underwent ROCM to give a 2.5:1 (*E*:*Z*) mixture of diastereomeric cyclic hydrazines. This substrate also appears to be a suitable precursor for ring-opening polymerization. The cycloadduct of 1,3-cyclopentadiene and an acyl nitroso compound underwent ROCM to give a mixture of four cyclic hydroxylamines. These results represent the first examples of ROCM on strained cyclic substrates containing multiple heteroatoms.

With the development of well-defined catalyst systems, olefin metathesis has emerged as an important method for the preparation of complex molecules and unique materials.[1] Ring-opening metathesis polymerization (ROMP) and ring closing metathesis (RCM) processes have received a great amount of attention as new synthetic methods.[1] However, the ring-opening metathesis of a strained cyclic substrate followed by cross metathesis with another alkene also holds great promise for the assembly of complex structures. Such ring-opening cross metathesis (ROCM) processes of various norbornene and cyclobutene derivatives have



Scheme 1.

Keywords: ring-opening cross metathesis; hetero-Diels–Alder; hydrazines; hydroxylamines.

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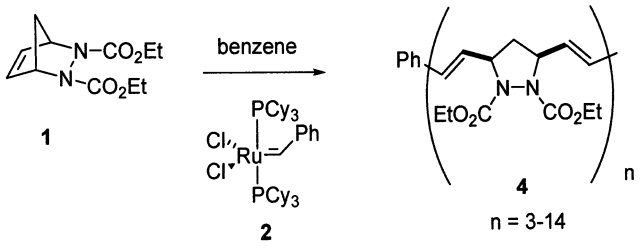


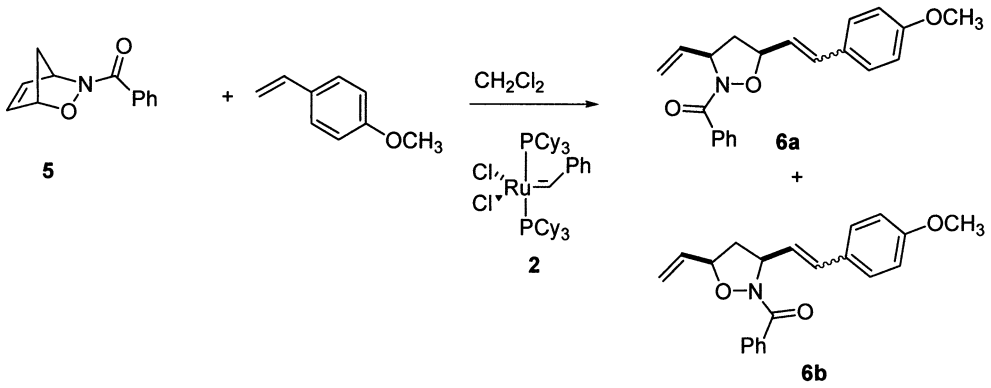
Scheme 2.

been described and have resulted in the total synthesis of multifidene and viridiene.[2–6] Recently, catalytic asymmetric ROCM has been developed and applied to the enantioselective synthesis of functionalized cyclopentanes.[7–10] We wish to communicate the first combination of the hetero-Diels–Alder reaction of 1,3-cyclopentadiene and N–N and N–O heterodienophiles to form strained [2.2.1] bicyclic systems containing two heteroatoms with ROCM to produce new functionalized heterocyclic five-membered rings.

Diels–Alder cycloaddition of 1,3-cyclopentadiene with diethyl azidodicarboxylate produces the symmetric [2.2.1] bicyclic substrate (**1**) that contains two nitrogen atoms in 96% yield. Slow addition of a mixture of **1** and 4-vinylanisole (2.0 equiv.) to a room temperature methylene chloride solution of the ruthenium based Grubb's catalyst (**2**, 2.5 mol%) forms the diastereomeric cyclic hydrazines **3a** and **3b** in a 2.5:1 (**3a**:**3b**) ratio in nearly quantitative yield (Scheme 1). Chromatographic separation gives analytically pure samples of **3a** and **3b** and NOESY NMR experiments and coupling constant analysis reveal that the major isomer (**3a**) contains a disubstituted olefin possessing the *E* configuration and that the minor isomer (**3b**) contains a disubstituted olefin of the *Z* configuration.[11] While terminal aromatic alkenes generally cross metathesize to produce the *E* isomers, examples of *E*/*Z* olefin mixtures have been noted.[4] Catalytic hydrogenation of a mixture of **3a** and **3b** produces a single product providing further evidence that **3a** and **3b** simply differ in the configuration of the disubstituted alkene. This result also indicates that **3a** and **3b** have maintained the *cis* relative stereochemistry of the alkyl groups. The corresponding [2.2.2] bicyclic substrate derived from the Diels–Alder reaction of 1,3-cyclohexadiene and diethyl azidodicarboxylate did not undergo ROCM under these conditions, presumably due to a lack of ring strain in the starting material. At this time, initial ring-opening of the [2.2.1] bicyclic substrate followed by cross metathesis of the resulting metal alkylidene with 4-vinylanisole appears the most likely mechanism for this conversion. While norbornene derivatives containing a single heteroatom have been found to undergo ROCM to produce tetrahydrofurans and pyrrolidinones, these results show that this process can be extended to strained substrates containing two heteroatoms to form, in this case, a cyclic hydrazine.[2,3]

Treatment of cycloadduct (**1**) with 2.5 mol% Grubb's catalyst in benzene at room temperature over 2 days forms a tan solid material upon precipitation from hexane. MALDI-TOF mass spectrometry of this solid clearly indicates a mixture of oligomers (**4**) of 3 to 14 units that are separated by the molecular weight of **1** (MW = 240, Scheme 2). These results suggest that multiple heteroatom containing compounds, such as **1**, could serve as building blocks for new materials.

Cycloadduct (**5**), prepared by the periodate oxidation of benzohydroxamic acid in the presence of 1,3-cyclopentadiene,[12] provides an opportunity to examine ROCM of a non-symmetric substrate containing multiple heteroatoms (Scheme 3). Slow addition of a mixture of **5** and 4-vinylanisole (2 equiv.) to a methylene chloride solution of **2** (2.5 mol%) forms a mixture of four cyclic hydroxylamines in nearly equal amounts in 57% yield (Scheme 3). NMR experiments indicate that the four compounds consist of the *E* and *Z* diastereomers of the two regioisomers (**6a**–**b**, Scheme 1). Similar to the results with **1**, the use of a terminal aromatic alkene as the cross metathesis partner did not control the *E*/*Z* selectivity. Flash column chromatography separates these four compounds into two groups of two compounds and catalytic hydrogenation of one of these sets of two compounds produces two new products indicating that these separated groups of compounds consist of a mixture of regioisomers rather than a mixture of



Scheme 3.

the *E* and *Z* diastereomers of a single regioisomer. While a number of asymmetric substrates show little regioselectivity in ROCM,[2,4,6] some regioselective examples exist and the steric environment of the substrate appears to play a major role in controlling regioselective ring-opening.[2,6]

Taken together, these results indicate that the combination of a hetero-Diels–Alder reaction with ROCM represents a viable pathway to new five-membered ring heterocycles. Specifically, these results show for the first time that [2.2.1] substrates containing two heteroatoms, such as **1** and **5**, undergo ROCM with the ruthenium catalyst (**2**) to produce unique substituted cyclopentane-derived hydrazines (**3a**–**b**) and hydroxylamines (**6a**–**b**). These highly functionalized products could be transformed into new conformationally restricted amino acid derivatives (by selective alkene oxidation) or stereochemically defined acyclic synthetic intermediates (by N–N or N–O bond cleavage). These substrates also appear to be suitable precursors for ROMP processes. Future experiments will focus on improving the synthetic utility of this sequence by improving both the stereoselectivity of the disubstituted alkene formation and the regioselectivity of the ROCM of asymmetric substrates by varying the catalyst, the steric environment of the substrate, and the cross metathesis alkene partner.

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11. For **3a**: R_f 0.25 (4:1 pentane:EtOAc) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 (d, 2H), 6.8 (d, 2H), 6.5 (d, 1H, $J=15.5$ Hz), 6.0 (dd, 1H, $J=14.3$, 6.9 Hz), 5.8 (m, 2H), 5.3 (d, 1H, $J=17.0$ Hz), 5.1 (d, 1H, $J=10.3$ Hz), 4.6 (broad m, 2H), 4.1 (m, 4H), 2.5 (dt, 1H), 1.9 (dt, 1H), 1.2 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 159.7, 137.3, 130.9, 129.7, 128.1, 126.2, 116.3, 114.4, 62.6, 61.2, 55.7, 40.6, 30.7, 30.1, 14.9; LRMS (ES) m/z 397 ([M+Na]$^+$). Anal. calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 63.23; H, 7.01; N, 6.94. For **3b**: R_f 0.32 (4:1 pentane:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 (d, 2H), 6.8 (d, 2H), 6.4 (d, 1H, $J=11.5$ Hz), 5.8 (m, 1H), 5.6 (dd, 1H, $J=11.5$, 9.5 Hz), 5.3 (d, 1H, $J=17.1$ Hz), 5.1 (d, 1H, $J=10.32$ Hz), 4.8 (broad s, 1H), 4.6 (broad s, 1H), 4.1 (m, 4H), 3.7 (s, 3H), 2.5 (dt, 1H), 1.8 (dt, 1H), 1.2 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 159.2, 136.8, 130.4, 130.1, 129.8, 129.2, 116.3, 114.2, 62.9, 62.4, 61.0, 57.1, 55.6, 41.3, 30.7, 30.1, 14.9; LRMS (ES) m/z 397 ([M+Na]$^+$). Anal. calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 62.19; H, 6.91; N, 6.75.
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